DOCKET NO.: ISIS-3561 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Bennett *et al.*

Serial No.: **09/315,292** Group Art Unit: **1635**

Filed: **May 20, 1999** Examiner: **M. Shibuya**

For: **COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS**

I, **Emma R. Dailey**, Registration No. **48,491** certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On December 18, 2001

Emma R. Dailey Reg. No. **48,491**

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Gregory E. Hardee, Ph.D., do hereby declare as follows:

1. From February 1996 until the present time, I have lead (currently as Vice President) Drug Drug Delivery Research & Pharmaceutical Development at Isis Pharmaceuticals, Inc. ("Isis"), in Carlsbad, California.

2. At Isis, I am responsible for drug delivery research and pharmaceutical development of antisense oligonucleotide therapeutics, including research and design of novel dosage forms to enhance the therapeutic profile of antisense oligonucleotides. I have developed new technology for the topical, aerosol and oral delivery of antisense oligonucleotides. I have a Ph.D. with a major in Pharmaceutics and a minor in Pharmacology and 20 years of experience in the areas of drug development, drug delivery technology and formulations and process development. My Curriculum Vitae is attached hereto as Exhibit A.

3. From February 1985 until January 1996, I was the Director of Drug Delivery Research & Development at the Upjohn Company, where I was responsible for research and development of novel dosage forms, developing protocols and methods for *in vivo* (pharmacokinetics and drug safety) and *in vitro* evaluation of drug delivery systems and final formulations, and developing specifications for materials and finished products.

4. From July 1980 until January 1985 I was an Assistant Professor in the Department of Pharmaceutics in the College of Pharmacy at The University of Georgia, where I was responsible for undergraduate and graduate education in pharmaceutics, physical pharmacy and pharmacokinetics.

5. I am an inventor of the subject matter of the 09/315,292 application ("the 292 application"), filed May 20, 1999. The inventions of pending claims of the 292 application are directed to, among other aspects, methods for the pulmonary administration of antisense nucleic acids.

6. The 292 application claims priority under 35 U.S.C. § 120 to several U.S. patent applications, including serial no. 07/801,168 ("the 168 priority application") which was filed November 29, 1991.

7. I have read the Advisory Action mailed in connection with the 292 application on June 4, 2001. I understand that Examiner in charge of the 292 application has questioned the claim for priority to the 168 priority application, asserting, among other things, that pulmonary delivery of antisense oligonucleotides would not have been predictable for one of skill in the art and that undue experimentation would have been required to deliver antisense oligonucleotides by pulmonary administration given the unpredictability of the antisense art and the lack of particular guidance and direction in applicant's alleged priority documents/patents.

8. I have read the 168 priority application, specifically, page 10, which provides that "oligonucleotides may be formulated in a pharmaceutical composition" which may then be "administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated." Among the methods disclosed is inhalation.

9. I was one of ordinary skill in the art of formulation of aerosol delivery agents at the time the 168 priority application was filed.

10. Aerosol therapy was known to those of skill in the art prior to November 20, 1991. For example, Exhibit B, which is a copy of Cawley, "Aerosolized Administration of Drugs: Possible Future Agents and the Role of the RCP", *RTMagazine*, Feb. 1999, p. 1-7, states that aerosol therapy has been a form of drug delivery since the 19th century.

11. Exhibit C, which is a copy of Clark, "Medical Aerosol Inhalers: Past, Present, and Future", Aerosol Science and Technology, 22:374-91 (1995), provides that introduction of a

suspension of fine particles for respiration and treatment using a nebulizer has been know for approximately the last forty or fifty years (*See id.* at p. 375, col. 2), and knowledge of the use of dry powder inhalers and pressured metered dose inhalers (pMDI) can be traced back to the early mid-1950's. (*See id.* at p. 375 & 382).

14. Exhibit D is a copy of "How to Take Your Medicines: Adrenergic Bronchodilators (Inhaled)", June 1991, http://www.fda.gov/bbs/topics/CONSUMER/CON00005.html. This reference enumerates many drugs (*e.g.*, bronchodilators, albuterol, bitolterol, epinephrine, isoetharine, isoproterenol, metaproterenol, pirbuterol and tertbutaline) that were known in the art in 1991 to be administered to the lungs using metered dose inhalers and nebulizers. (*See* p.2 last para. & p.4)

15. Exhibit E is a copy of Kohler, "Aerosols for Systematic Treatment, " Lung (1990) Suppl. 677-684, which provides additional examples of the variety of compounds known to be administered by aerosols at the time of filing the 168 priority application. For example, Table 1 provides several different categories of agents for pulmonary administration, including antibiotics and antiviral agents, immunosuppressive agents, antielastase, vaccines, surfactant, protease, antitumor agents and anticold agents. (*See* p. 679).

16. The references discussed above demonstrate that in 1991, the art pertaining to inhalation of therapeutics was well developed, and those of skill in the art at that time knew how to formulate and deliver a wide variety of compositions for therapeutic and/or diagnostic purposes.

17. As such, those of ordinary skill in the art at the time the 168 priority application was filed, reading the disclosure in the 168 priority application, would have been able to formulate and deliver oligonucleotides, including antisense oligonucleotides, to the lungs for such purposes.

18. I declare that all statements made herein are of my own knowledge true and statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Gregory E. Hardee, Ph.D.

11/8/01